New treatments for prostate cancer

Introduction

- the number of prostate cancer patients is growing
- although metastatic prostate cancer is incurable, it is increasingly treatable
- the outlook for patients with metastatic prostate cancer is expected to improve further
- several treatment options have been developed this century, but many are similar
- lowering testosterone levels is currently the mainstay of treatment, but over time prostate cancer cells can become insensitive to low testosterone levels (castration resistance)
- new treatments with unique mechanisms are urgently needed

What do we need?

New medicines with a unique mode of action. Some examples are:

- targeted therapy: PARP inhibitors (olaparib)
- radioligand therapy (177Lu-PSMA)
- new testosterone receptor inhibitors (opevesostat)
- antibody-drug conjugates: ADC (ifinatamab deruxtecan)
- bispecific T-cell engagers: BiTEs (xaluritamig)

Targeted therapy: PARP inhibitors

DNA breaks are repaired perfectly by BRCA1/2. However, BRCA1/2 does not work in approximately 15% of prostate cancer patients. These patients depend on the PARP protein for DNA repair. When PARP is inhibited by olaparib, DNA damage in tumour cells cannot be repaired while in healthy cells less DNA damage occurs. For patients with a proven BRCA1/2 gene mutation for whom previous treatment with testosterone-lowering therapy was unsuccessful, olaparib improves quality of life and prolongs survival. Side effects include damage to blood production, fatigue and nausea. Several PARP inhibitors are under development, including talazoparib, niraparib and rucaparib. Research into the efficacy of olaparib in the castration-sensitive stage is ongoing.

Radioligand therapy: 177Lutetium-PSMA

Prostate-specific membrane antigen (PSMA) enables a one-to-one relationship between imaging and therapy. PSMA tracers are absorbed by cells with PSMA. Depending on the radioactive particle linked to the PSMA tracer, the radiation emitted by the particle can be used for imaging (PSMA-PET scan) or therapy (irradiating prostate cancer cells from within). Patients with a 'good PSMA-PET scan' are eligible for PSMA therapy. The most common radioactive particle used for this purpose is 177Lutetium, other options are 225Actinium, 227Thorium, 213Bismuth and 212Lead. 177Lu-PSMA appears to be effective in half of patients, improving quality of life and prolonging survival for patients previously treated with testosterone-lowering therapy and chemotherapy. Side effects are usually mild, but damage to blood production, fatigue, nausea

and dry mouth are common. 177Lu-PSMA is an important addition to treatment options. Currently, it is still only available in a limited number of Dutch hospitals as a 'last line' treatment, but PSMA-targeted therapy is undergoing rapid development, with extensive research being conducted into 177Lu-PSMA therapy in earlier stages, even in the very early stages.

New testosterone receptor inhibitors

Only testosterone can bind to an androgen receptor, and testosterone is produced in stages. For patients with testosterone-sensitive prostate cancer, drugs that inhibit the final stage in the production of testosterone are currently available. However, abnormalities can occur in the receptor, allowing also precursors of testosterone to bind to the receptor. Opevesostat inhibits testosterone production at an early stage, and research is currently being conducted to determine its added value for this patient group. Previous studies have shown that prostate-specific antigen (PSA) levels decreased significantly in 70% of patients with an abnormal testosterone receptor. While the side effects are limited, adrenal gland failure is possible, which can have serious consequences.

Antibody-drug conjugates: ADC

Prostate cancer cells have B7-H3 on their surface. Ifinatamab deruxtecan is an antibody-drug conjugate that binds to B7-H3. It is absorbed to the cell, where the drug is released and then damages the DNA. Ifinatamab deruxtecan may be effective against multiple tumour types. However, little is known about its potential activity in prostate cancer patients. Side effects include damage to blood production, fatigue and nausea.

Bispecific T cell engagers: BiTEs

Prostate cancer cells have STEAP on their surface, while T cells have CD3. T cells are ‘cell-killing immune cells’ that attack prostate cancer cells. Xaluritamig is a T-cell engager that recognises both STEAP and CD3 and then sticks the T-cell and prostate cancer cell together. Promising results have been achieved with xaluritamig in a small group of patients, and xaluritamig is now being investigated as a treatment for castration-resistant prostate cancer. Previous research has already shown promising results in prostate cancer patients who have undergone multiple previous treatments, in about half of the patients PSA decreased significantly. Side effects include fatigue and muscle pain, and cytokine release syndrome occurs in 70% of patients. This syndrome can be dangerous, with flu-like symptoms and organ failure.

Conclusions

- lowering testosterone levels is currently the mainstay of treatment options
- new treatments with unique mechanisms are urgently needed
- to this end, research has been done on various classes of drugs that are already available, or in development